## REMARKS

Applicants respectfully request reconsideration in view of the foregoing amendments and the following remarks.

### Claim Status

Claim 25-31 are canceled without prejudice or disclaimer.

Claim 24 is amended to clarify the claim language and reflect the elected subject matter, in accordance with discussions with the Examiner during the recent Patent Office and Telephone Interviews. Support for the recitation of "non-hypoxic conditions" is found, for example, at page 4 of the specification as filed, which discusses growth under normal oxygen conditions in contrast to growth under hypoxic conditions.

Claim 24 also is amended to recite the phenotype of "shoot branching" as set forth, for example, at page 12 of the specification as filed. Dependent claim 36 is added to recite this embodiment, and it also is recited in new claim 37.

Claims 33-37 are added to recite specific embodiments of the elected subject matter. New claims 33-37 find support throughout the as-filed application and original claims, *e.g.*, in original claim 24..

No new matter is added by these amendments.

Applicants reserve the right to pursue any canceled subject matter in one or more continuing applications with the same rights of priority as the instant application.

Following entry of these amendments, claims 24 and 33-37 will be pending. These claims are presented for examination.

### Applicants' Statement Of Substance Of Interviews

Applicants thank Examiners Worley and Grunberg for the helpful discussions and suggestions made during the Patent Office Interview held June 29, 2011, as well as follow-up Telephone Interviews of June 30, 2011 and July 15, 2011.

As reflected in the Interview Summary mailed July 8, 2011, inventor Dr. Hill, Applicant's Representatives, and Examiners Worley and Grunberg discussed the rejections of record.

With regard to the § 112, second paragraph, rejection, Applicants suggested replacing the term "normal oxygen conditions" with "non-hypoxic conditions," and Examiner Worley indicated that would be acceptable. This amendment is included in the amendments presented above.

With regard to the § 112, fist paragraph, rejections, Dr. Hill explained that it would not have required any undue amount of experimentation for a skilled artisan to practice the claimed invention with regard to the use of the barley non-symbiotic hemoglobin gene used in the examples, because there was one known gene and its full-length sequence was known and published before the present application's priority date. With regard to the scope of the claims generally, Dr. Hill explained that the non-symbiotic hemoglobin gene family is highly conserved throughout nature, both in structure and function, and that the alfalfa plants used in the examples are representative of plants generally.

During a follow-up Telephone Interview on June 30, 2011, Examiner Worley and Applicant's representative discussed proposed claim language and evidence that would help advance prosecution, including some of the claim amendments presented above and the types of papers submitted herewith.

During a follow-up Telephone Interview on July 13, 2011, as summarized in the Examiner Interview Summary mailed July 15, 2011, Examiner Worley and Applicant's representative discussed proposed claim language that might advance prosecution, contingent upon Applicants' ability to overcome the enablement rejection with evidence of the conserved nature of non-symbiotic hemoglobin sequences across the plant kingdom.

These issues are addressed more fully below.

**The Application Data Sheet**

The Office Action indicates that the Application Data Sheet (ADS) submitted April 18, 2007 incorrectly references PCT/IB2004/004119, rather than PCT/IB2004/004419. Office Action, item 2, page 4. Applicants thank Examiner Worley for noting this typographical error, which the attached Supplemental ADS remedies.

**Claim Objection**

Claim 24 was subject to objection for reciting non-elected subject matter. The foregoing amendments obviate this issue. As noted above, Applicants reserve the right to pursue non-elected embodiments in a continuing application with the same priority rights as the present application.

**Rejections Under 35 U.S.C. § 112, Second Paragraph (Indefiniteness)**

Claims 24, 28, 30, and 32 were rejected under 35 U.S.C. § 112, second paragraph, for alleged indefiniteness in the recitation of "normal oxygen conditions." Without acquiescing on the merits, and as discussed during the Interviews, the instant claims are amended to recite that plants are grown under "non-hypoxic conditions." As the July 8, 2011 Examiner Interview Summary indicates that this amendment would be acceptable to overcome the rejection, Applicants believe that the rejection is now overcome.

**Rejections Under 35 U.S.C. § 112, First Paragraph (Enablement)**

Claims 24, 28, 30, and 32 were rejected under 35 U.S.C. § 112, first paragraph, for alleged lack of enablement. Office Action, item 5, pages 5-14. Specifically, the Office Action alleges that the specification does not enable the full scope of the claims because (1) the application does not disclose the barley non-symbiotic hemoglobin cDNA used in the antisense constructs; (2) Applicants only demonstrate the claimed methodology in transgenic alfalfa and therefore do not enable all plants; and (3) the state of the art is such that one cannot predict the tissue-specificity or function of non-symbiotic hemoglobins. These issues were thoroughly discussed during the Patent Office Interview, and are further addressed by the comments and references submitted herewith. In particular, Examiners Worley and

Grunberg invited Applicants to submit evidence that the barley non-symbiotic hemoglobin sequence was known and that non-symbiotic hemoglobin sequences are conserved accross plant species, evidence of which Applicants are submitting herewith.

**(1) The Barley Non-Symbiotic Hemoglobin Sequence Was Known In The Art**

As Dr. Hill explained during the June 29th Interview, the sequence of the barley non-symbiotic hemoglobin cDNA was known in the art and available to the public before the present application's priority date. For example, Dr. Hill's laboratory published the barley non-symbiotic hemoglobin cDNA sequence in Taylor *et al.*, *Plant Molecular Biology* 24:853-862 (1994) (submitted herewith).

**(2) Alfalfa Is A Model Plant System For The Claimed Methods**

As discussed during the June 29th and July 13th Interviews, the alfalfa plants used in the working example are an accepted model plant system for many transgenic plant methods. While Dr. Hill selected alfalfa primarily based on its availability and relevance as a commercial crop, there is nothing unique about alfalfa that would prevent results obtained with alfalfa from being extrapolated to other plants. This is particularly true in the context of the present invention, in view of the ubiquitous nature of non-symbiotic hemoglobin, as discussed in more detail below.

Accordingly, the illustrative alfalfa model used in the examples enables the full scope of the claims, as the illustrative model is predictive of the effect one would expect to achieve using others plants.

**(3) Non-Symbiotic Hemoglobin Is Ubiquitous And Conserved**

Although the Office Action characterizes the non-symbiotic hemoglobin art as "unpredictable," as taught in the specification and discussed during the Interviews, non-symbiotic hemoglobin is ubiquitous in the plant kingdom and has the same primary function in all plants.

The Office Action cites papers directed to antisense methodologies generally, and alleges that they show that antisense suppression is highly unpredictable, especially for multi-gene families. Office Action, page 9 (citing Colliver *et al.* (1997) and Elomaa *et al.* (1996), which do ***not*** pertain to non-symbiotic hemoglobin). However, as discussed during the June 29th Patent Office Interview, the non-symbiotic hemoglobin family actually is highly conserved as to both function and structure.

As taught in the specification, non-symbiotic hemoglobin is somewhat unique in that it is found throughout nature and has a specific, primary function: binding ligands. That is, regardless of the host organism in which the non-symbiotic hemoglobin resides or sequence variations among non-symbiotic hemoglobin sequences of various origin, all non-symbiotic hemoglobins have the primary function of binding ligands. Because non-symbiotic hemoglobin has a specific and conserved function, antisense suppression of non-symbiotic hemoglobin would be expected to exhibit predictable effects across the plant kingdom, such as by modifying the recited plant phenotypes.

As discussed during the Interviews, non-symbiotic plant hemoglobins also exhibit substantial sequence similarity. For example, as shown in Andersson *et al.* (1996), an alignment of plant hemoglobin sequences from various plants revealed highly conserved residues and regions, including regions of conservation in promoter sequences as well as the placement of intron sequences. *See* Andersson *et al. Proc. Natl. Acad. Sci. USA* 93:5682-5687 (June 1996) (copy attached), Figures 1 and 5. Notably, Andersson demonstrates in Figure 1 that substantial sequence similarity exists in non-symbiotic hemoglobins even across monocot (e.g., rice) and dicot (e.g., soybean) plants. *Id.* at page 5683. Similar findings were reported in Trevaskis *et al. Proc. Natl. Acad. Sci. USA* 94:12230-12234 (October 1997) (copy attached). Thus, non-symbiotic hemoglobin is conserved both functionally and structurally across the plant kingdom.

**(4) Antisense Suppression Does Not Require 80% Sequence Homology**

As discussed during the June 29th Interview, Applicants believe that some of the Examiner's concerns stem from a misunderstanding as to the degree of sequence homology

required for antisense suppression. For example, the enablement rejection was based in part on the Examiner's BLAST searches, which failed to identify non-symbiotic hemoglobin sequences with at least 80% homology. However, such a high degree of homology is not required for antisense suppression.

Although Applicants were not able to identify references directly addressing antisense suppression, Applicants believe that work done with microRNA and small RNA is relevant in this regard. As illustrated in Mallory et. al., *Trends in Plant Science* 13: 35967 (2008) and Karginov et al., *Proc. Nat'l .Acad. Sci.* 104: 19291-96 (2007) (copies attached) micro and small RNAs form sense/antisense duplexes with target RNA sequences that initiate the formation of nucleases that degrade target RNA sequences that have been transcribed. The micro/small RNA, usually as an antisense construct, binds to the sense RNA, forming the duplex that initiates the degradation. The micro/small RNAs are usually 20-22 base pairs in length and while there is some requirement for homology, they do not necessarily have to have high homology. This shows that the formation of sense/antisense duplexes does not require a high degree of homology across a full-length sequence, but only some homology across shorter sequences, such as some homology across 20 base pair-regions.

Applying this principle in the context of the present invention means that the antisense methodology can work even if heterologous cDNA sequences share less than 80% homology across the entire sequence. Indeed, this is demonstrated by the examples which demonstrate efficacy using a barley non-symbiotic hemoglobin sequence in alfalfa plants.

Comparing the full-length barley and alfalfa (Medicago sativa) (and other plant) non-symbiotic hemoglobin cDNA sequences, it is apparent that there are regions with 66% or greater homology, including a number of regions longer than 20-22 bases in which the homology is greater than 75%. Thus, this degree of homology is sufficient for operability of the recited methods.

In further support of enablement, Applicants note that their earlier patent, U.S. 6,936,749 (already of record), demonstrates the suppression of non-symbiotic hemoglobin in maize cells transformed with a barley non-symbiotic hemoglobin sequence in

antisense orientation. *See* '749 patent, Figures 2-5. This experiment shows that the homology between barley and maize non-symbiotic hemoglobin also is sufficient for antisense suppression.

Thus, the teachings in the specification, including the examples with barley non-symbiotic hemoglobin and alfalfa, are sufficient to enable the full scope of the pending claims with regard to the ability of a heterologous antisense plant non-symbiotic hemoglobin to reduce expression levels of non-symbiotic hemoglobin in a host plant and confer a modified plant phenotype, as demonstrated in the examples set fort in the application.

**(4) The Arrendondo-Peter Paper Does Not Support The Rejection**

The Office Action cites Arrendondo-Peter *et al.* (*Plant Physiol.* 1998), for the proposition that "one of skill in the art cannot predict the tissue-specificity or function of non-symbiotic hemoglobins." Office Action, page 8. Specifically, the Office Action cites Arrendondo-Peter for teaching:

> Some non-symbiotic hemoglobins are expressed in root meristems and vasculature, whereas others are expressed in rosette leaves, and others in leaves, and others in leaves and roots. Some are induced by low temperature, some by hypoxic conditions, some may be regulated by calcium-dependent protein kinases.

However, as discussed during the Patent Office Interview, the cited passages of this reference relate to ***natural*** expression of ***endogenous*** non-symbiotic hemoglobins, and do not undermine enablement of the claimed methods, where a plant includes an expression vector comprising a nucleotide sequence encoding a plant non-symbiotic hemoglobin in antisense orientation.

Applicants also understand that some of the Examiner's concerns in this regard stemmed from the manner in which she was reading the previous claims (*e.g.*, as requiring every transformed plant to exhibit every modified phenotype), which is believed to be obviated by the instant claim amendments (*e.g.*, the "selecting" language).

Applicants also note that Arrendondo-Peter is not contemporaneous with the priority date of this application, as it was published in 1998. Thus, it is not valid as evidence of the state of the art.

In view of the foregoing, the teachings provided in the specification fully enable the skilled artisan to practice the full scope of the pending claims. Applicants therefore believe that the pending enablement rejections have been overcome and should be withdrawn.

**Rejections under 35 U.S.C. § 112 (Written Description)**

Claim 24, 28, 30, and 32 were rejected under 35 U.S.C. § 112, first paragraph, for alleged lack of written description. Office Action, item 6, pages 14-19. While acknowledging that the specification describes transgenic alfalfa plants transformed with antisense constructs comprising a barley non-symbiotic hemoglobin, the Office Action alleges that the written description requirement is not satisfied because the application (1) does not set forth the barley cDNA used in the examples, (2) includes only alfalfa examples, and (3) does not describe antisense constructs other than those used by Dordas *et al.* and Howa *et al.* which include barley non-symbiotic hemoglobin." *Id.* at page 16. The Office Action therefore concludes that "the specification fails to provide an adequate written description to support the genus of antisense constructs effective for altering shoot or root apical dominance, shoot branching, flower color, or chlorophyll content as set forth in the claims." *Id.* at paragraph spanning pages 18-19. Applicants respectfully traverse these rejections.

Applicants note that the written description rejections largely mirror the enablement rejections, and so are believed to be addressed above.

To the extent that the written description rejections stem from alleged shortcomings of the disclosure *per se*, Applicants emphasize that the specification objectively describes the invention in terms commensurate with the scope of the claims. Moreover, as shown above, the specific examples included in the specification are representative of the full scope of the pending claims. Thus, the specification as a whole demonstrates Applicants' possession of the full scope of the methods recited in the pending claims.

For at least the foregoing reasons, it is believed that the pending written description rejections have been overcome, and should be withdrawn.

**Rejections under 35 U.S.C. § 103**

Claims 24, 28, and 30 were rejected under 35 U.S.C. § 103 (a) as allegedly obvious over Dordas *et al. The Plant Journal* 35:763-770 (2003). Office Action, item 7, pages 19-21. Specifically, the Office Action cites Dordas for disclosing transgenic alfalfa root cultures transformed with non-symbiotic hemoglobin antisense constructs. *Id.* at page 20. While admitting that Dordas does not teach transforming a ***whole plant*** or modifying a resultant plant ***phenotype***, the Office Action alleges that it would have been obvious to regenerate a whole plant from the transgenic root cultures. *Id.* Applicants respectfully traverse this rejection.

This obviousness rejection is improper for several reasons.

First, as recognized in the Office Action, Dordas does not establish a prima facie case of obviousness, as it provides no teaching, suggestion or reason to grow, under non-hypoxic conditions, a plant that comprises an expression vector comprising a nucleotide sequence encoding a plant non-symbiotic hemoglobin in antisense orientation, and then select a plant exhibiting a modified plant phenotype selected from shoot or root apical dominance; shoot branching; flower color; and chlorophyll content.

The Office Action asserts that it would have been obvious from Dordas to transform a whole plant to "allow studying the phenotype in tissues other than root tissues," but this mischaracterizes Dordas. Dordas does not teach or suggest that transformation with antisense non-symbiotic hemoglobin has ***any*** impact on ***any plant phenotype***. Rather, Dordas reports the impact on ***root growth rate***. Indeed, because Dordas teaches the benefits of ***over-expression*** of non-symbiotic hemoglobin in order to maintain root growth rate under hypoxic conditions, Dordas provides no reason whatsoever to carry out a method as claimed.

Second, the claimed methods achieve unexpected results that could not have been predicted or expected from Dordas. In particular, there is no indication in Dordas that a

method that includes growing, under non-hypoxic conditions, a plant that comprises an expression vector comprising a nucleotide sequence encoding a plant non-symbiotic hemoglobin in antisense orientation, would result in a plant exhibiting a modified plant phenotype selected from shoot or root apical dominance; flower color; shoot branching; and chlorophyll content, as recited in the instant claims.

Thus, applying the standards reflected in *KSR v. Teleflex*, 127 S. Ct. 1727, 1739 (2007), the obviousness rejection is improper and should be withdrawn.

## CONCLUSION

Applicants believe that the application is in condition for allowance, and respectfully request an early indication of same.

If there are any questions regarding this submission, or if any issues remain, Examiner Worley is invited to contact the undersigned by telephone in order to advance prosecution.

Respectfully submitted,

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The Commissioner is authorized to charge any unpaid fees required in this application, or credit any overpayment, to Deposit Account No. 19-0741. If any extensions of time are needed, Applicant hereby petitions for such extension under 37 C.F.R. §1.136 and authorizes payment from Deposit Account No. 19-0741.